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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/388,899	09/02/1999	BEREND HOUWEN	10690/T/B/A	4619

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EXAMINER	
GABEL, GAILENE	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 08/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/388,899	HOUWEN ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7-14 and 16-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *16 and 17* is/are allowed.

6)☒ Claim(s) *1-3,7-14 and 18* is/are rejected.

7)☒ Claim(s) *4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Withdrawal of Restriction Requirement

1. Upon further consideration, the restriction requirement mailed to Applicant on 4/6/04 in light of the newly submitted claims, is being withdrawn.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/1/04 has been entered.

Amendment Entry

3. Applicant's amendment and response filed 3/1/04 is acknowledged and has been entered. Claims 5, 6, and 15 have been cancelled. Claims 16-18 have been added. Accordingly, claims 1-4, 7-14, and 16-18 are pending and are under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-3, 7-14, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bowen et al. (Laboratory Hematology, 1997) in view of Gopinath et al. (Cytometry, 1997).

Bowen et al. teach patterns of expression of CD16 and CD11b antigens by cells in bone marrow of patients using flow cytometric monoclonal antibody-based, three color immunofluorescence technique which permits simultaneous characterization of different cell populations (see Abstract). In flow cytometric analysis studies, Bowen et al. teach aspirating a hematological sample (bone marrow) into blood collection tubes, staining the cells using a combination of three different monoclonal antibodies, then lysing erythrocytes using Ortho Lyse. Specifically, Bowen et al. teach staining the sample with the combination of fluorescent labeled antibodies including 1) fluorescence-labeled CD45 antibody (first fluorescence-labeled antibody), fluorescence

isothiocyanate (FITC)-labeled CD16 antibody (second fluorescence-labeled antibody), and phycoerythrin (PE)-labeled CD11b antibody (third fluorescence-labeled antibody). Five parameters were measured flow cytometrically which include side angle scatter (SALS), forward angle scatter (FALS), Tri-color fluorescence intensity, FITC intensity, and PE intensity. In data analysis, a gate was set to classify immature (developing) and mature fluorescence-labeled granulocytes, which have high side angle scatter, thus, excluding other leucocytes that are not granulocytes (blasts, monocytes, and lymphocytes), and which have lower side angle scatter. From the granulocyte gate, events were also quantified in fluorescence intensity measurements of the cells labeled with FITC-labeled CD16 antibody and PE-labeled CD11b antibody (see page 294, column 1). Bowen also confirmed that peripheral blood neutrophil populations within varying maturation levels (promyelocytes, myelocytes, metamyelocytes, and band cells) are quantified within the CD11b and CD16 regions because both CD16 and CD11b normally increase during the maturation of granulocytes from promyelocytic stage to segmented neutrophil stage (see page 294, column 2 and page 275, column 1). Bowen further observed that the manual percentage of band to segmented neutrophils correlated well with CD16 expression suggesting that in the course of granulocyte maturation, CD11b expression appears earlier and prior to the expression of CD16; therefore, anti-CD16 antibodies are more useful in defining granulocytes in later maturation stages than CD11b (see page 296, column 2). In conclusion, Bowen teach that simultaneous quantitation of SALS and fluorescent labeled monoclonal antibody

binding to CD45, CD16, and CD11b define highly reproducible developmental maturation patterns of the granulocytic cell population series in flow cytometry.

Bowen et al. differ from the instant invention in failing to teach distinguishing eosinophils and neutrophilic cells in the granulocytic cells measured in step 4) of claim 1 on the basis of the intensity of fluorescence from the first fluorescence-labeled antibody and the intensity of fluorescence from the second or third fluorescence-labeled antibody, as recited in step 5) in claim 1. Bowen et al. also differ from the instant invention in failing to teach staining leucocytes after the erythrocytes are removed from the hematological sample.

Gopinath et al. teach identification of eosinophils in lysed whole blood samples utilizing their high side angle scatter and intensity of fluorescence-labeled CD16 antibody; specifically, CD16 fluorescence intensity negativity (see Abstract). According to Gopinath, use of lysed whole blood in flow cytometry allows the study of cell surface markers on cell populations such as granulocytes, lymphocytes, and monocytes without using cell purification techniques that may affect expression of these markers. In study, Gopinath et al. teach using PE labeled anti-CD16 to distinguish neutrophils from eosinophils. CD16 is expressed uniformly in immature to mature neutrophilic stages (metamyelocyte, band, and segmented neutrophils); by contrast, eosinophils are CD16 negative. Additionally, eosinophils display a high side angle scatter in comparison to neutrophils (see page 313, columns 1-2). Specifically, Gopinath et al. teach that the most accurate isolation of eosinophils from neutrophils is obtained by a combination of side angle scatter and anti-CD16 PE fluorescence intensity (see page 314, column 1).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Gopinath in distinguishing between neutrophils and eosinophil populations, with the flow cytometric method as taught by Bowen because Gopinath specifically taught that CD16 fluorescence negativity in addition to side angle scatter measurement provides for accurate isolation of eosinophils from neutrophils in granulocytic populations and Bowen specifically taught obtaining fluorescence intensity measurements of fluorescence-labeled anti-CD45 and anti-CD16 to define granulocytic populations which include both neutrophils and eosinophils, in early maturation stages. One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the teaching of Gopinath in lysing hematological samples prior to performing the flow cytometric method taught by Bowen which assesses expression of cell surface markers such as CD45, CD16, and CD11b, because Gopinath specifically taught that use of lysed hematological samples, i.e. whole blood, in flow cytometry allows the study of cell surface markers on cell populations of granulocytes, lymphocytes, and monocytes without using cell purification techniques that may affect expression of these markers.

Response to Arguments

5. Applicant's arguments filed 3/1/04 have been fully considered but they are not persuasive.

A) Applicant argues that Bowen does not teach "distinguishing eosinophils and neutrophils in the granulocytic cells ... on the basis of the intensity of fluorescence from the first fluorescence-labeled antibody and the intensity of fluorescence from the second fluorescence-labeled antibody and the combination of Bowen with Gopinath does not suggest nor render obvious the same teaching since Gopinath also lacks such disclosure. Applicant specifically contends that both Bowen and Gopinath neither teach nor suggest using two fluorescence-based antibodies.

Contrary to Applicant's argument, Bowen teaches performing flow cytometric analysis of three cell surface markers, CD45, CD16, and CD11b using fluorescent-labeled antibodies including a first fluorescence-labeled antibody (fluorescence-labeled CD45 antibody), a second fluorescence-labeled antibody (FITC-labeled CD16 antibody), and a third fluorescence-labeled antibody (PE-labeled CD11b antibody) in a three color immunofluorescence technique, which permits simultaneous characterization of different cell populations. Bowen uses flow cytometry to analyze angle scatter and fluorescence intensity measurements of all of fluorescence-labeled antibodies to enable classification of leucocytes and granulocytes (both mature and immature). Gopinath is incorporated with the teaching of Bowen for the teaching of distinguishing eosinophils from other granulocytes in lysed whole blood samples utilizing their high side angle scatter and intensity of fluorescence-labeled CD16 antibody. Specifically, Gopinath teaches that eosinophils exhibit CD16 fluorescence intensity negativity in flow cytometric analysis using PE labeled anti-CD16 in comparison to neutrophils. It would have been obvious to one of ordinary skill in the art

at the time of the instant invention to incorporate the teaching of Gopinath in distinguishing eosinophils from neutrophil populations, with the flow cytometric method as taught by Bowen because Gopinath specifically taught that eosinophils exhibit CD16 fluorescence negativity in addition to high side angle scatter which provides for accurate isolation of eosinophils from neutrophils in granulocytic populations and Bowen specifically taught obtaining fluorescence intensity measurements of fluorescence-labeled anti-CD45 and anti-CD16 in defining granulocytic populations, which include both neutrophils and eosinophils, in early maturation stages. Accordingly, the combination of Bowen with Gopinath suggests step 5) of claim 1 which recites "distinguishing eosinophils and neutrophilic cells in the granulocytic cells ... on the basis of the intensity of fluorescence from a first fluorescence-labeled antibody (anti-CD45) and the intensity of fluorescence from a second or third fluorescence-labeled antibody (anti-CD16), as recited in step 5) in claim 1.

While Gopinath, indeed, uses a combination of side angle scatter and fluorescence intensity measurement of fluorescence labeled anti-CD16 antibody to distinguish eosinophils from neutrophils, the current claim recitation does not exclude use of side angle scatter in making a distinction between eosinophils and other granulocytic populations. Accordingly, the combination of Bowen and Gopinath is said to render obvious the claimed invention.

B) Applicant argues that neither Bowen nor Gopinath discloses "classifying and counting" neutrophilic cells, as recited in the claims and that Bowen is only concerned

with left-shift scatterplot patterns and Gopinath is directed to isolation of eosinophils. According to Applicant, the objectives of Bowen and Gopinath differ, and as such, neither citation is concerned with classification and counting of neutrophils within maturation groups, and there is no evidence showing motivation to do the same.

In response, "classification and counting" of leucocytic populations having distinct cell surface markers including CD45, CD16, and CD11b, are an inherent property and capacity in flow cytometric analysis, which enables identification between numerous distinct populations. Bowen identified cell surface expressions of each one of CD45, CD16, and CD11b in leucocyte and granulocyte (both mature and immature) populations and Gopinath identified cell surface expression of eosinophil populations, both in congruent with flow cytometry. As such the recitation of "classification and counting" in the rejected claims, reads on and/or is suggested by the combined teaching of Bowen and Gopinath.

Allowable Subject Matter

6. Claims 16 and 17 are allowable.

7. Claim 4 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703)

305-0807. The examiner can normally be reached on Monday, Tuesday, and Thursday, 7:30 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-0169.

Gailene R. Gabel
Patent Examiner
Art Unit 1641
July 19, 2004

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641
8/2/04